Adverse reactions after large-scale treatment of onchocerciasis with ivermectin: combined results from eight community trials

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Eight community trials were carried out by the Onchocerciasis Control Programme in West Africa to determine the safety of the new microfilaricide ivermectin during large-scale treatment of onchocerciasis. The trial areas were located in eight different countries and varied greatly in endemicity level; a total of 50 929 persons were treated and monitored for 72 hours. Overall treatment coverage was 60% of the census population, the main reasons for non-treatment being the exclusion criteria. Of those treated, 9% reported with adverse reactions, 2.4% with moderate reactions, and 0.24% with severe reactions. Most reactions were reported during the first day of follow-up, the most frequent severe reaction being severe symptomatic postural hypotension (in 49 cases). Three cases of severe dyspnoea were life-threatening but their relationship with ivermectin treatment is uncertain. The incidence of adverse reactions was directly related to skin microfilarial load and was highest in the foci with the highest endemicity levels. Treatment resulted in 98% reductions in mean microfilarial loads at all endemicity levels. The benefit of treatment largely compensated for the discomfort due to adverse reactions, which were all transient and managed successfully. Ivermectin thus appears to be sufficiently safe for large-scale treatment but monitoring by resident nurses for at least 36 hours is recommended.

Introduction

Ivermectin, a new microfilaricide for the treatment of human onchocerciasis (*1*), has been shown to be highly effective and relatively well-tolerated in a series of clinical trials (*2–6*). The drug's registration for human use in October 1987 in France was of major significance for the Onchocerciasis Control Programme in West Africa (OCP) which, from the start of its operations in 1975 (*7*), used to rely on vector control through larviciding as the sole available method of control. However, as only 1209 selected volunteers had been treated with ivermectin during the clinical trials (*8*), further evidence was needed that the drug was sufficiently safe to be used on a large-scale in endemic areas which had limited health care facilities for dealing with possible severe adverse reactions. The Onchocerciasis Control Programme therefore undertook, between August 1987 and May 1988, eight community trials to determine (1) the safety of ivermectin for large-scale treatment and (2) its potential for transmission control (*12*). The combined results on the adverse reactions encountered during these eight trials are reported here. The first results of the effect on transmission are reported elsewhere (*13*).

Materials and methods

Trial areas

The trial areas represented the different epidemiological situations of operational importance for the OCP and ranged from non-controlled hyperendemic foci in the extension areas to foci with incomplete control in the original programme area. For the purpose of the transmission component of the study, relatively isolated onchocerciasis foci with a local transmission cycle were selected. Fig. 1 shows the location of the selected trial areas. Their main characteristics are summarized in Table 1 which lists the trials in chronological order of ivermectin treatment. Four of the trials, i.e., in Asubende, Milo,

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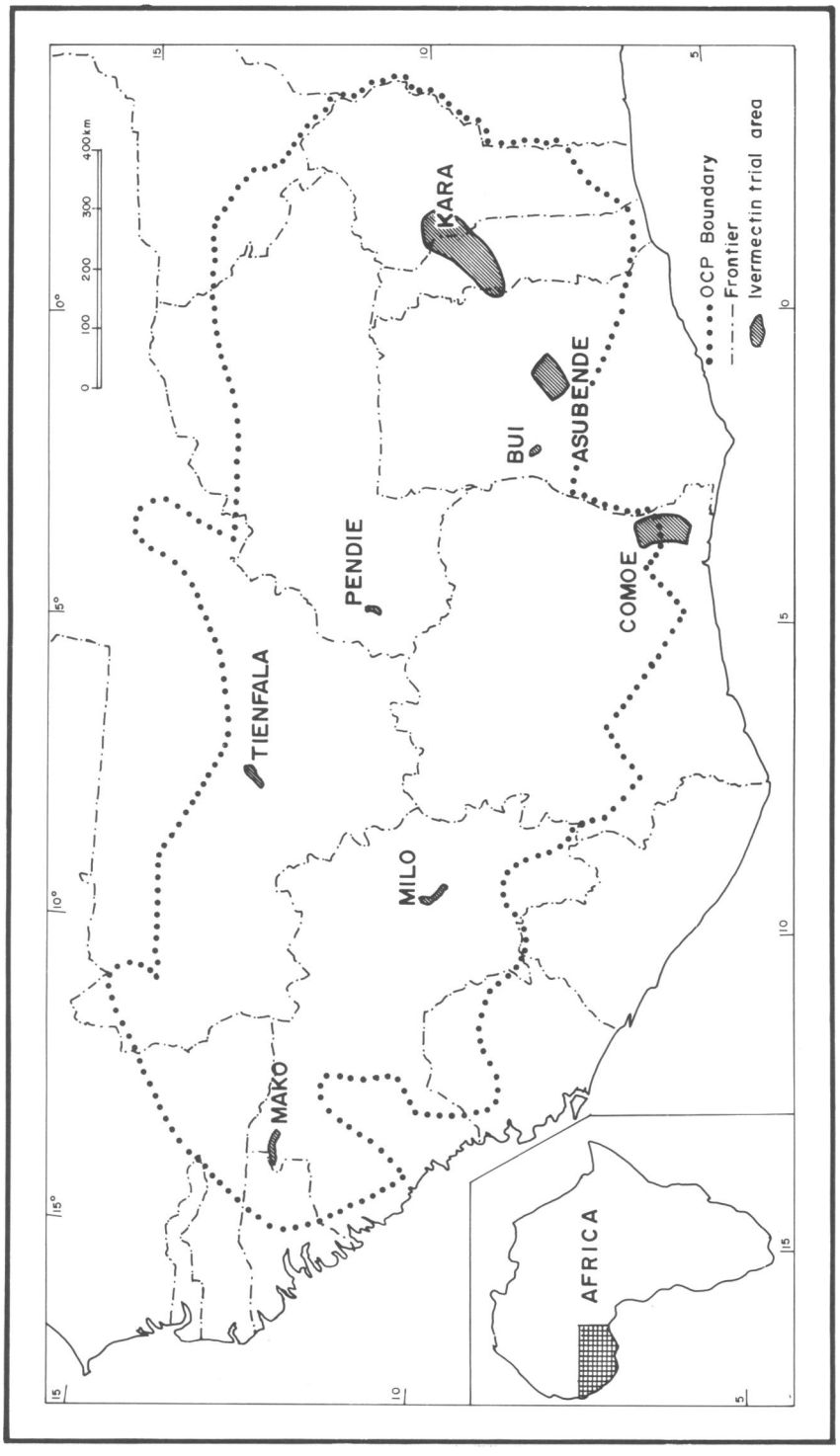


Fig. 1. **Location of the trial areas in West Africa.**

Table 1: **Description of the trial areas**

Place	River	Previous vector control	Percentage population distribution by village CMFL[a]			Total population
			<10 mf/snip	10–35 mf/snip	>35 mf/snip	
Bui, Ghana	Black Volta	Control since 1975; incomplete interruption of transmission	90	10	0	1573
Asubende, Ghana	Pru	No control till 1986	49	42	9	26 117
Kara, Togo and Benin	Kara/ Kéran/Mô	Control since 1977, reinvaded by infective flies	90	6	4	21 437
Comoe, Côte d'Ivoire	Comoe	Selective control of savanna flies; no control of forest flies	100	0	0	22 575
Pendie, Burkina Faso	Dienkoa	Control since 1975; localized relapse in transmission	100	0	0	2965
Milo, Guinea	Milo	No control till 1987	26	64	9	3659
Tienfala, Mali	Niger	No control	65	27	8	4435
Mako, Senegal	Gambia	No control	74	17	9	4802

[a] Community microfilarial load (CMFL) in mf/snip.

Tienfala and Mako, took place in hyperendemic onchocerciasis foci in the extension areas of the OCP where the epidemiological situation had not been affected by vector control. The Comoe trial was located in the pre-forest area on the southern boundary of the OCP where transmission is mainly due to the forest vector *Simulium sanctipauli* s.l. The other three trials, located within the original programme area, were in foci where an insufficient level of control had been achieved, either because of reinvasion by infective flies from elsewhere (Kara), or because of the difficulty of local larviciding (Bui), or because of undetected local vector breeding and a subsequent relapse in transmission (Pendie).

Epidemiological mapping and endemicity levels

Skin-snip surveys were done in a sample of villages in each trial area. This involved a complete village census, the taking of two skin snips from the iliac crest of each person using a Holth corneoscleral punch, and the microscopic examination of the skin snips for *Onchocerca volvulus* microfilariae after 30 minutes incubation in distilled water (*9*). These results were used to determine the endemicity level of the village as expressed by the community microfilarial load (CMFL), i.e., the geometric mean number of microfilariae per snip (mf/snip) in persons aged $\geqslant 20$ years (*10*). A map was made for each trial which showed the geographical distribution of onchocerciasis endemicity and the CMFL values for non-surveyed villages were estimated by extrapolation. Table 1 shows the approximate distribution of the population by endemicity level of the village. The endemicity level was lowest in Comoe and Pendie where the total population lived in villages with CMFLs below 10 mf/snip. The most endemic areas in the study were the populous Asubende region where over 50% of the population lived in villages with a CMFL in excess of 10 mf/snip, and Milo where nearly three quarters of the population fell in this category.

Organization of ivermectin delivery

The health ministries of the eight participating countries collaborated in these trials and provided additional medical personnel. Guidelines for drug distribution and monitoring together with specially designed data collection forms were prepared and all personnel were briefed before the start of field activities in each area. A major effort was made to ensure maximum, voluntary, community participation. Local authorities were informed, in advance, of the purpose and nature of the trials and of the need for informed consent. The trial areas were divided into sectors, each assigned to a medical officer who was responsible for ivermectin distribution and the monitoring of adverse reactions.

Drug administration

Following a census by a trained census clerk, the community members were requested to present themselves as family units at the treatment post. They

were questioned about being pregnant, whether lactating (and for how long), and about any family history of epilepsy. A rapid examination of each patient was conducted with regard to general health and the presence of anaemia, jaundice, oedema, high fever (by touch), and multiple facial injuries that may suggest epilepsy. Selected patients were examined for neck stiffness. Local officials assisted in obtaining informed consent to treatment. Ivermectin was administered as a single oral dose, based on body weight, to all those who agreed to treatment and were not excluded by the following criteria: age under 5 years old, body weight of less than 15 kg, pregnancy, lactating women (during first three months; in Bui and Asubende, only the first month), jaundice, severe anaemia, disease of the central nervous system, and any other severe illness. The treated patients were advised to avoid undue physical activity and to refrain from consumption of alcoholic drinks for the following 72 hours.

Adverse reactions

Monitoring. Monitoring of adverse reactions was carried out usually by nurses living in the villages for at least 72 hours after the treatment. Only in the three largest trials was a section of the population, who lived in very dispersed settlements, monitored by mobile nurses who visited each settlement at least once per day. Patients were requested to report with any complaint to the monitoring nurse. After the second trial in Asubende, patients were advised to stay at home in case of dizziness and general weakness, and to send a relative to fetch the nurse. Symptoms were always volunteered by the patient and not sought by questioning.

Quantification. In order to classify the severity of the various types of reaction a system of quantifying, principally addressed to nurses as the primary personnel involved in monitoring, was developed (Table 2). This was a simplification of the protocol used by the Onchocerciasis Chemotherapy Research Centre (*11*). Four grades of reactions were recognized: no reaction, mild, moderate, and severe reaction. The grading of reactions was based on the functional disability experienced by the patient at the time of the medical examination. Thus, mild reactions involved symptoms but not disability, moderate reactions showed symptoms with partial disability, and severe reactions had symptoms with complete functional disability. Two exceptions to this general rule were:

- Fever, in which an arbitrary age-dependent scale was used irrespective of disability. The cut-off age between children and adults was 12 years. In children an axillary temperature of 38.5–39.4 °C was defined as moderate fever and $\geqslant$ 39.5 °C as severe fever. In adults the corresponding temperatures were 39.5–40.4 °C and $\geqslant$40.5 °C.
- Rash, which was graded as mild when it covered less than one third of the body surface and moderate when it was more extensive; a severe rash was considered inappropriate since it did not carry any element of disability.

Data processing and analysis. All data processing was performed on microcomputers equipped with removable mass storage devices. The analysis of treatment and adverse reaction data was done using SPSS/PC+ and with BMDPC for logistic regression analysis. The results from the skin-snip surveys were processed using routine OCP computer programs.

Table 2: **Grading of common reactions as mild, moderate and severe**

Symptom	Mild	Moderate	Severe
Itching[a]	Not obviously scratching; no scratch marks	Obvious recent scratch marks or excoriations; insomnia, but remained in bed; able to carry out normal activity at reduced level	Vigorous continuous scratching, restless insomnia with abandonment of bed and pacing up and down
Joint pain Muscle ache Gland pain Backache	No discomfort, normal gait	Obvious marked limp or difficulty in moving about	Rooted to the spot (pillar of salt); bedridden on account of any of these symptoms
Headache[b]	Comfortable	In distress, holding head stiffly	Restless, bedridden
Swollen limb	Only part of limb; no pain or mild pain only	Whole limb ± pain, plus some impairment of normal use	Whole limb and adjacent areas ± pain, plus loss of normal use

[a] If there is a rash, its location and extent should be noted.
[b] Neck stiffness, fever and any change in mental state should be checked.

In order to facilitate the presentation of results on adverse reactions, a number of reaction types with common features were grouped together as follows:

- Painful conditions: headache, joint pain, muscle aches, general aches, backache.
- Gland reaction: pain or swelling.
- Fever: fever, chills.
- Swelling: limbs, face, other sites except glands.
- Cutaneous reaction: itching, rash.
- Ocular reaction: pain, redness, watering.
- SSPH (severe symptomatic postural hypotension); defined as the inability of a patient to stand for at least two minutes owing to severe dizziness or weakness attributable to a marked drop in the blood pressure.
- Dyspnoea: asthma, laryngeal oedema.
- Other complaints: anorexia, nausea, vomiting, dizziness, insomnia.

Results

Treatment coverage

Table 3 shows the treatment coverage by trial area. The coverage was fairly uniform and varied from 59.3% to 67.7% in seven of the trials; the lowest coverage (55%) was obtained in Comoe where the population was very dispersed and highly mobile. The coverage was higher in the smaller trial areas (population of less than 5000) than in the three large trials with populations of over 20 000. The only exception was in Tienfala where there was much mobility owing to proximity to the national capital. The most frequent cause of non-treatment was age (less than 5 years) (43.6%) followed by failure to present at the treatment post (38.5%), mainly because of absence from the village. Pregnancy and lactation (first three months) accounted for 6.4% of exclusions from treatment, and severe illness and epilepsy for 1.8%.

Table 3: **Ivermectin treatment coverage by trial area**

Trial area	Total population	No. treated
Bui	1573	1065 (67.7)[a]
Asubende	26 117	14 991 (61.5)[b]
Kara	21 437	12 924 (60.3)
Comoe	22 575	12 436 (55.1)
Pendie	2965	1390 (63.4)[b]
Milo	3659	2327 (63.6)
Tienfala	4435	2632 (59.3)
Mako	4802	3164 (65.9)
Total	87 563	50 929 (59.9)[b]

[a] Figures in parentheses are percentages.
[b] Excluding villages where only skin-snip positives were treated.

Severe adverse reactions

The incidence of severe adverse reactions in the total treated population, by trial area, is shown in Table 4. The most frequent severe reaction encountered was severe symptomatic postural hypotension (SSPH) which was diagnosed in 49 patients. However, three of the five cases from Kara were not confirmed by the supervising medical officer. The majority (37) of SSPH cases were diagnosed in Asubende but not one was detected during the last four trials where, instead, four cases of severe dizziness were reported. These differences between the trials are partly a result of changes in the monitoring procedure for SSPH. In the first two trials all treated persons were asked to report any complaints at the monitoring station

Table 4: **Number of severe adverse reactions, including severe symptomatic postural hypotension (SSPH), by trial area**

Trial area	No. treated	All severe reactions	SSPH	SSPH or severe dizziness	Severe fever	Severe dyspnoea	Severe pain
Bui	1065	1 (0.94)[a]	1 (0.94)	1 (0.94)	0	0	0
Asubende	14 991	52 (3.47)	37 (2.47)	37 (2.47)	13 (0.87)	2 (0.13)	0
Kara	12 924	10 (0.77)	5 (0.39)	5 (0.39)	5 (0.39)	0	0
Comoe	12 436	20 (1.61)	6 (0.48)	6 (0.48)	11 (0.88)	1 (0.08)	2 (0.16)
Pendie	1390	3 (2.16)	0	0	3 (2.16)	0	0
Milo	2327	4 (1.72)	0	3 (1.29)	1 (0.43)	0	0
Tienfala	2632	2 (0.76)	0	1 (0.38)	1 (0.38)	0	0
Mako	3164	1 (0.32)	0	0	0	0	1 (0.32)
Total	50 929	93 (1.83)	49 (0.96)	53 (1.04)	34 (0.66)	3 (0.06)	3 (0.06)

[a] Figures in parentheses indicate the incidence rate per 1000 population.

which was centrally located in the village. Following the unexpectedly high incidence of SSPH in Asubende, where several cases actually collapsed at the monitoring post, all treated persons were advised in the subsequent trials to lie down in case of dizziness or general weakness and to send for the nurse. It is most likely that this change in procedure reduced the incidence of SSPH by eliminating the physical stress of walking to the monitoring station in patients who were already dizzy and weak. Furthermore, the operational definition of SSPH requires that a patient should attempt to stand for more than two minutes while the blood pressure is being taken. However, based on the previous experience with SSPH, it was decided in the last four trials not to request patients who felt very dizzy to stand up; potential SSPH cases were consequently no longer diagnosed.

Treatment in the form of a single dose of 200 mg of hydrocortisone sodium succinate was given to nine SSPH cases. These included a lightly infected (25 mf/snip) 27-year-old woman whose blood pressure and pulse could not be detected by the examining nurse. Another woman of the same age had an imperceptible pulse and a blood pressure of 70/40 mmHg, but she remained alert all the time. The other seven patients either looked ill or had a recurrence of SSPH on retesting 5–12 hours later. All nine patients improved, usually within 2–4 hours, and were able to sustain an adequate standing blood pressure.

There were three cases of severe dyspnoea—one with laryngeal oedema and two with severe asthma in known asthmatics—occurring within 24 hours after ivermectin treatment and requiring prompt, intense medical intervention. A pre-treatment skin biopsy was taken from only one of the severe asthma cases and the snips were negative. Severe fever was more frequent in children, in part because of the lower cut-off point used in this age group. All cases of severe fever and severe pain responded to treatment with paracetamol or paracetamol and chloroquine.

Adverse reactions in villages with resident monitoring

Only the villages monitored by nurses who were resident for the full 72 hours' monitoring period were included in the analysis of the incidence of adverse reactions of all grades of severity. This is because mild and moderate reactions would probably have been underreported in the villages with mobile nurses during their brief visits one or more times per day.

Type of reaction. In the villages with resident nurses a total of 31 260 people were treated with ivermectin and 2815 of them (9%) reported with one or more adverse reactions (Table 5). The most frequent reactions were pain, followed by cutaneous reactions, fever, swelling and gland reactions; most of these were classified as mild. The proportion of reactions classified as moderate was higher for gland reactions than for the other types. The group of 'other complaints' covered a variety of reactions, dizziness being the most common.

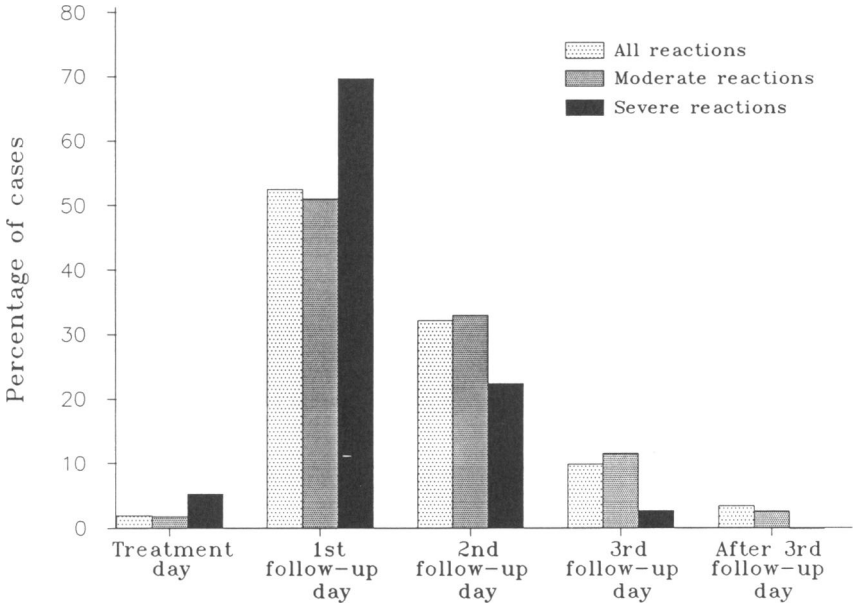
Hardly any adverse reactions occurred during the day of treatment itself; more than half were reported on the next day after treatment, the incidence of reactions decreasing progressively during the subsequent days of monitoring (Fig. 2). The proportion of reactions reported during the first day of follow-up was much higher for severe reactions since 80% of the SSPH cases and all the severe dyspnoea cases were reported then. There was not much difference in the time of reporting between the other type of reactions even though gland reactions and swellings appeared to be slightly delayed.

Table 5: **Incidence of different types of adverse reaction after ivermectin treatment in villages with resident monitoring (number treated: 31 260)**

Type of reaction	All levels of reaction	Moderate reaction	Severe reaction
Pain conditions	1746 (5.59)[a]	253 (0.81)	2 (0.006)
Cutaneous reactions	945 (3.02)	218 (0.70)	0
Fever and chills	824 (2.64)	209 (0.67)	28 (0.090)
Swelling	809 (2.59)	118 (0.38)	0
Gland reactions	354 (1.13)	146 (0.47)	0
Eye reactions	116 (0.37)	5 (0.02)	0
SSPH or severe dizziness	46 (0.15)	0	46 (0.147)
Dyspnoea	11 (0.04)	0	1 (0.003)
Other complaints	464 (1.48)	21 (0.07)	0
Most severe reaction	2815 (9.01)	745 (2.38)	76 (0.243)

[a] Figures in parentheses are percentages.

Fig. 2. **Day of first reporting of adverse reactions. Villages with resident monitoring only ($n=2815$ cases with reaction).**



Relationship with intensity of infection. The relationship between the incidence of adverse reactions and the intensity of infection was studied in 7239 treated patients from six trial areas for whom pre-treatment skin snip results were available. Fig. 3 shows that the incidence of reactions was directly related to the mf load in the skin. The incidence of severe, moderate, and all reactions increased from 0.1%, 0.3% and 2.7% in the skin-snip-negative group to 2.3%, 11.4% and 35.8%, respectively, in people with >128 mf/snip; the relationship is highly significant for all three grades of severity (logistic regression analysis: $P < 0.001$ in each case). It may be noted that the severe reactions in the skin-snip-negative group concerned four cases of severe fever. An equally clear relationship was observed for painful conditions, fever, gland reactions, other reactions, and to a lesser extent for swelling ($P < 0.001$ in each case). However, cutaneous reactions showed a quite different pattern. They were significantly more frequent in skin-snip positives compared to skin-snip negatives ($P < 0.001$), but within the skin-snip-positive group there was no increase in cutaneous reactions with increasing mf load ($P=0.83$) and the lowest incidence was actually observed in the group with the highest intensity of infection. SSPH and severe dizziness are shown together in Fig. 3 and, even though the number of cases involved is small, their combined incidence as well as the incidence of SSPH alone were also significantly related to the intensity of infection ($P<0.001$).

Variations between trial areas. The incidence of adverse reactions ranged from low rates of 4.8%, 5% and 6% in Kara, Pendie, and Comoe, via intermediate values of 7.9% in Mako and 9.5% in Tienfala, to high rates of 14.9% in Asubende and 15.7% in Milo. This variation correlates well with the ranking of the endemicity levels of the trials (see Table 1) and suggests that the differences may be due to variations in intensity of infection between trials. The results on adverse reactions were therefore also compared between trials after correction for intensity of infection; the results are shown in Fig. 4. In each trial area there was a statistically significant relationship between the incidence of adverse reactions and skin mf load ($P<0.001$). The relationships were similar but the incidence of adverse reactions in Milo was significantly higher than in the other areas ($P<0.001$). In Comoe there appeared to be a slower increase in adverse reactions with intensity of infection but the mf loads in this trial were low and the difference was only of borderline significance ($P=0.032$). There was no difference between the other trials ($P=0.83$).

Ivermectin dosage. The body weight and the number of ivermectin tablets were recorded for each person and the exact ivermectin dosage taken could be

Fig. 3. **Incidence of different types of adverse reactions in relation to skin microfilarial load. Villages with resident monitoring only ($n=7239$).**

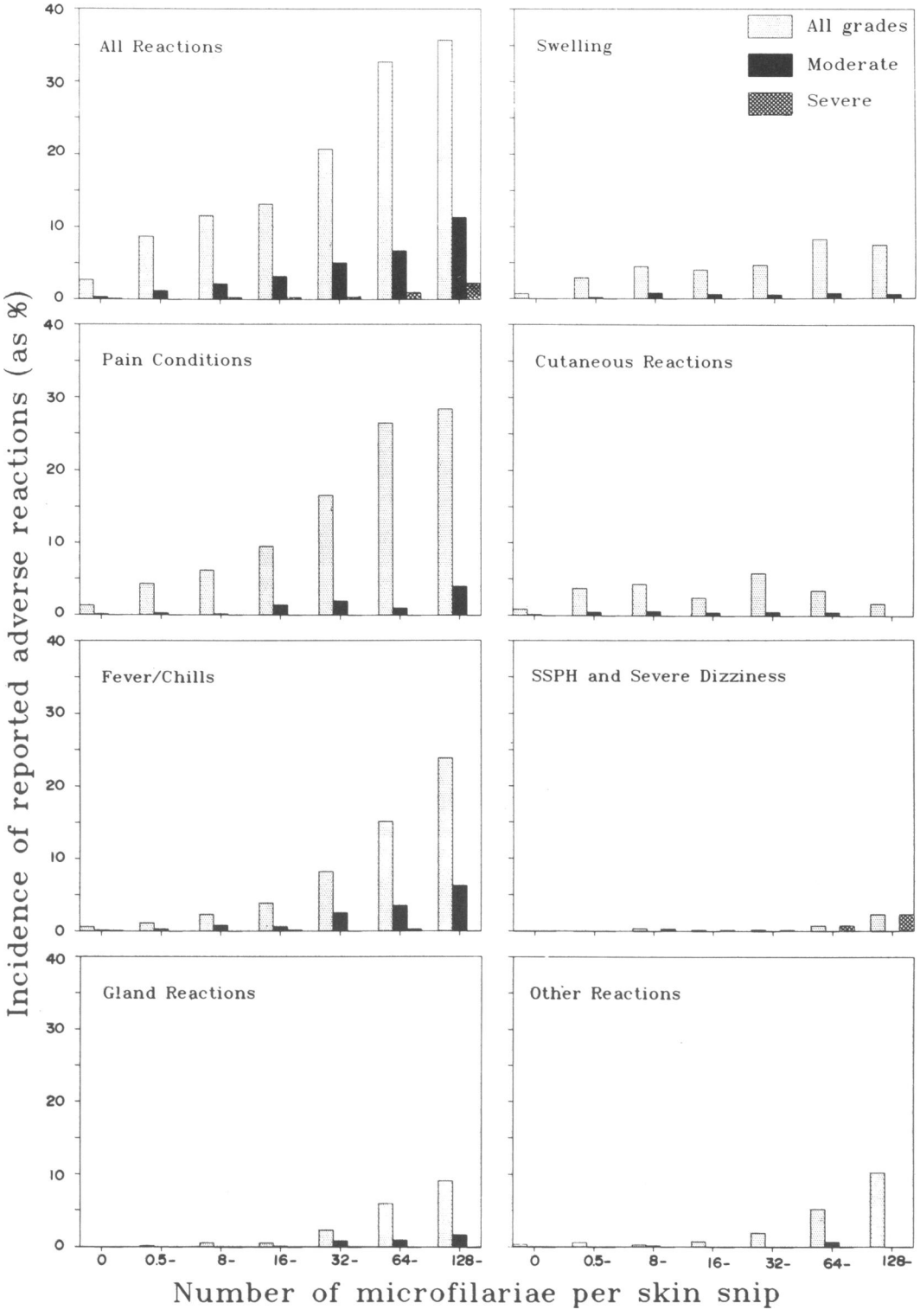
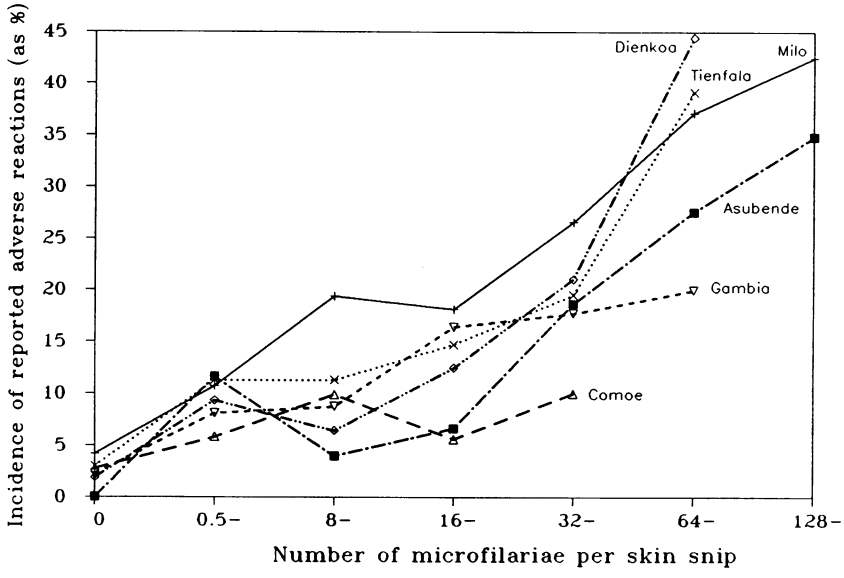


Fig. 4. **Incidence of adverse reactions in different trial areas in relation to skin microfilarial load. Villages with resident monitoring only ($n=7239$).**



calculated. The dosage ranged from 100 to 200 μg/kg in children and from 130 to 200 μg/kg in adults. After correction for mf load there was a statistically significant relationship between the incidence of all reactions and ivermectin dosage ($P<0.001$), but no such relationship existed for moderate reactions ($P=0.84$) or for severe reactions ($P=0.63$). The implication of this finding is illustrated in Fig. 5 which shows the incidence of adverse reactions by dosage in 15 601 persons aged > 20 years. This age limit was introduced to eliminate the confounding effect of intensity (*10*). The figure shows that there is indeed an increase in the total incidence of adverse reactions with ivermectin dosage but the difference in incidence between the lowest and highest dosage group is very small.

Delayed reactions and mortality

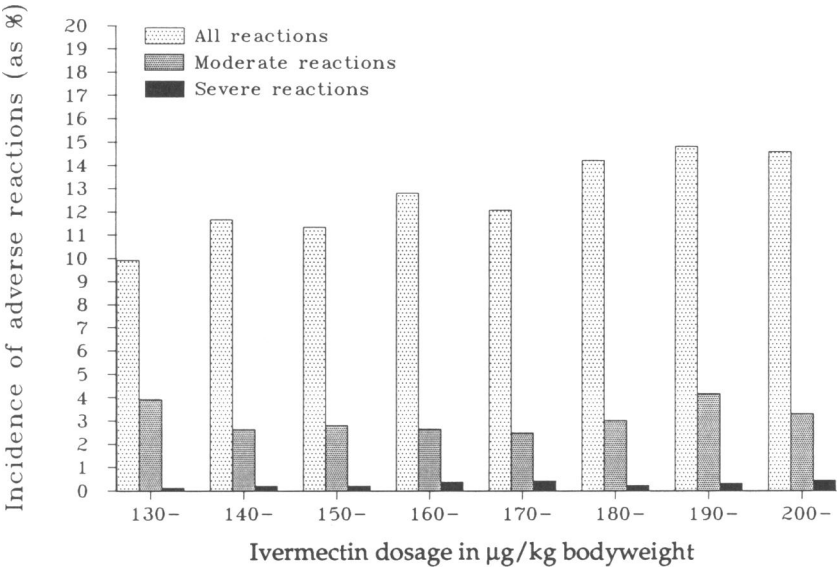
Delayed reactions refer to those that occurred after the 72-hour monitoring period and the departure of the monitoring team. During a 4-week follow-up visit in the Asubende trial area a total of 13 people reported delayed reactions. Because of this finding a follow-up visit was undertaken in each of the six remaining trials two weeks after ivermectin distribution. The most frequent delayed reaction was swelling (19 cases) which was reported in five areas. In Asubende five cases with abscesses and one with pyoarthrosis were seen (*12*), but none from the other areas. A case of delayed gland reaction was reported in three areas. Two patients were hospitalized for pulmonary infections. Two cases of joint pain and one each with paraesthesia, fever and abortion were also reported.

None of the 50 929 persons treated with ivermectin was reported to have died during the 72-hour-monitoring period and only one death was reported during the follow-up visit. This concerned a 38-year-old male who, according to his wife, had had an episode of generalized pain, perspiration and marked weight loss two weeks before ivermectin distribution. On the treatment day (14 April 1988) he had walked to the treatment post where he received the ivermectin. Two days later he reported with chest pain to the monitoring nurse and was treated with paracetamol. Fever started on 18 April after the departure of the monitoring team and lasted until this death on 23 April. His relatives attributed his death to a condition called "white jaundice" which, according to the local nurses, refers to acute anaemia caused by malaria or another infectious disease.

Microfilaricidal effect by endemicity level

Follow-up skin snip surveys were carried out in selected villages from three of the trial areas in order to study the microfilaricidal effect of ivermectin for different endemicity levels; the results are shown in Table 6. Three villages were selected from the Asubende trial area and these were the most endemic villages from all the eight trials. The CMFL, which is

Fig. 5. **Incidence of adverse reactions in relation to ivermectin dosage in adults aged 20 years or above. Villages with resident monitoring only (n=15 601).**



based on skin snip counts for adults, was as high as 64.4 mf/snip and the pre-treatment geometric mean count in treated patients from all age groups was equal to 45.4 mf/snip. A sample of less infected but still hyperendemic villages was followed up in the Milo area. Finally, several villages were included from the Pendie area where the endemicity level was very low. Table 6 shows the changes in skin microfilarial loads which were seen in treated patients two weeks after treatment in Milo and two months after treatment in Asubende and Pendie. In the Asubende trial more than half of the skin-snip positives had become negative after treatment, while in the Pendie trial more than 90% of skin-snip positives had reverted. On the average there was a reduction of about 98% in skin mf loads; this reduction was similar for the different endemicity levels and certainly not less pronounced in the most endemic villages. In each of these three trial areas there were a few cases, representing some 2–3% of patients with high mf loads, who responded poorly or not at all to ivermectin treatment.

Discussion

The community trials of ivermectin were an exceptional effort. The OCP managed to treat and monitor

Table 6: **Reductions in skin mf loads in treated patients from follow-up villages in three trial areas with different endemicity levels**

Trial area	Endemicity level[a]	No. treated and followed up	Prevalence (%) of mf		Geometric mean mf/snip		
			Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Percentage reduction
Asubende	64.4	497	93.0	44.3	45.43 (39.64–52.05)[b]	0.70 (0.58–0.84)	98.5
Milo	18.3	549	83.2	22.6	11.90 (10.26–13.79)	0.25 (0.20–0.31)	97.9
Pendie	3.2	416	43.8	4.1	1.42 (1.13–1.73)	0.04 (0.02–0.06)	97.3

[a] As measured by community microfilarial load (CMFL).
[b] Figures in parentheses are the 95% confidence intervals.

over 50 000 people within less than a year and another five community trials are being undertaken by investigators from outside the OCP area. The overall treatment coverage in the OCP trials was 60% of the census population. The lowest coverages were obtained in areas with the most mobile populations where there was a high rate of absenteeism at the time of treatment. The main reasons for non-treatment were the exclusion criteria, and particularly the minimum age limit of 5 years. In our opinion it is unlikely that coverage can be greatly increased without major changes in the existing exclusion criteria.

Ivermectin treatment showed a dramatic microfilaricidal effect, as in the clinical trials (*1–6*), and reduced the skin microfilarial loads by some 98%. The percentage reduction was the same over a wide range of endemicity levels, the drug being equally effective in villages with the highest endemicity where large-scale treatment is most indicated because of the high risk of onchocercal eye lesions and blindness. A few subjects did not respond to ivermectin, probably owing to malabsorption of the drug, but these cases will be studied in detail during the second round of treatment.

The total incidence of adverse reactions was much lower in the community trials than in the clinical trials (*8*). This is not surprising, given the differences in the treated populations and monitoring procedures, i.e., passive field monitoring in communities where treatment was given irrespective of infection, compared with regular clinical examinations of hospitalized patients who all had moderate to severe infections. However, the types of reaction were generally similar and included various pain conditions, fever, itching, rash, lymph node enlargement, and oedema. Not reported previously were inguinal gland pain and brawny oedema of the limbs, which were fairly common in the most endemic trial areas where gland pain could be a significant cause of morbidity lasting for several days.

The incidence of adverse reactions was directly related to the skin mf load. This strongly suggests that the observed reactions were due to the microfilaricidal effect of ivermectin and not to the drug's intrinsic toxicity or to some other disease for which the population was seeking medical help. The relationship with skin mf load was significant for all the different types of adverse reactions with the exception of cutaneous reactions which were more frequent in skin-snip positives but for which there was no increase in incidence with increasing mf load. The relationship with intensity of infection explains why adverse reactions were much more common in the most endemic areas. After correction for intensity of infection there was a similar incidence of adverse reactions in all trial areas. Only in Milo did the incidence of reactions remain higher. The differences between type of reactions in their relationship with mf load explain the differences in the pattern of reactions between areas. Cutaneous reactions did not increase with the mf load and were therefore relatively common in areas with the lowest endemicity but ranked only fifth in the most endemic areas. On the other hand, the incidence of gland reactions started to increase only for high mf loads and these reactions were almost exclusively found in foci of high endemicity. Within the observed ivermectin dosage range of 100 to 200 μg/kg there was no relation between moderate or severe reactions and dosage, but mild reactions were less common in the lower dosage range. However, the difference was very small and it seems unlikely that a major reduction in adverse reactions can be achieved by reducing the dosage without severely limiting the microfilaricidal effect of the drug.

Most of the reported adverse reactions were mild, transient and required no treatment. All moderate reactions, with the exception of gland reactions, responded well to simple treatment with paracetamol, promethazine or chloroquine. A total of 93 severe adverse reactions were reported; the most common was severe symptomatic postural hypotension, diagnosed in 49 cases, nine of which were treated with an intravenous injection of hydrocortisone with immediate improvement, usually within two to four hours. The other SSPH cases recovered without treatment after several hours of rest in the supine position. Severe fever was the second most common severe reaction and all cases were successfully managed by treatment with paracetamol or paracetamol and chloroquine. SSPH and severe fever both showed a statistically significant relationship with the intensity of infection, which indicates that SSPH and most of the severe fevers were definitely adverse reactions to ivermectin treatment.

The three cases of severe dyspnoea were life-threatening and occurred within 24 hours of taking the ivermectin in three villages with relatively low endemicity levels. This condition had not been reported in the clinical trials. One patient with laryngeal oedema had an upper respiratory tract infection prior to the ivermectin treatment, which may have led to the severe episode. He was found to have a lobar pneumonia subsequently. This was the only reported case of oedema of the upper respiratory tract of any degree of severity and a causal relation with ivermectin treatment is doubtful. Two episodes of severe asthma occurred in known asthmatic patients; a pretreatment skin snip had been taken from one of them and no microfilariae were detected. Two mild attacks at asthma were also reported in

known asthmatics. The possibility that ivermectin treatment precipitates asthmatic attacks in known asthmatics cannot be excluded and this question should receive further attention during future treatments with ivermectin.

Virtually no adverse reactions were reported on the day of treatment itself. However, more than half of all the adverse reactions, two thirds of the severe ones, 80% of SSPH cases, and all three severe dyspnoea cases were reported during the first day after treatment. Only a small number of cases, with mainly mild reactions, were reported during the third follow-up day so that the monitoring period of 72 hours could be reduced during future large-scale treatment with ivermectin. A few delayed reactions were reported during follow-up visits after two to four weeks but their relation with ivermectin treatment was doubtful. Only for swelling, which was the most common delayed reaction, is it likely that such a relationship exists because it was reported in several trial areas.

No deaths were reported among treated persons during the 72-hour-monitoring period and only one death, for which there was no indication of a relationship with ivermectin treatment, was reported during the follow-up visits. This number of deaths is far below what would be expected normally in a population of this size during a two-week period. One explanation for this discrepancy is that most deaths occurred in people who were already severely ill at the time of ivermectin distribution and who were therefore excluded from ivermectin treatment. However, it is also possible that a number of deaths were not reported during the follow-up visits.

These results on adverse reactions in more than 50 000 treated persons from endemic onchocerciasis foci indicate that ivermectin is sufficiently safe to be used for large-scale treatment of onchocerciasis. All the adverse reactions were transient and were managed successfully by the monitoring teams. The discomfort of these adverse reactions was more than compensated by the massive reductions in mf loads in the treated patients and by the corresponding decrease in the risk of developing onchocercal complications (7). It has been shown above that the incidence of adverse reactions is also related to the intensity of infection. This implies that the benefit of ivermectin treatment will be greatest in those communities where adverse reactions are most frequent. The incidence and severity of adverse reactions will be much lower in the less endemic areas and probably also in hyperendemic areas during a second treatment after six to twelve months when the mf loads in treated patients will not yet have returned to the pretreatment levels. The few medical emergencies that occurred were in patients from villages with relatively low levels of endemicity. We therefore recommend that large-scale treatment with ivermectin should involve monitoring by resident nurses for a period of at least 36 hours after treatment in any onchocerciasis focus, whatever the level of endemicity.

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Résumé

Réactions indésirables à la suite d'un traitement à grande échelle de l'onchocercose par l'ivermectine; résultats globaux de huit expériences communautaires

Le Programme de lutte contre l'onchocercose (OCP) en Afrique de l'Ouest a entrepris huit expériences communautaires d'utilisation de l'ivermectine, un nouveau microfilaricide. Ces expériences avaient deux objectifs principaux: déterminer l'innocuité du médicament dans le traitement à grande échelle de l'onchocercose et évaluer son potentiel comme moyen de lutte contre la transmission de la maladie. Les essais ont eu lieu dans huit pays d'Afrique de l'Ouest différents par la situation épidémiologique et le niveau d'endémicité de l'onchocercose. Le présent article expose les résultats obtenus en ce qui concerne les réactions indésirables précoces.

Au total, 50 929 personnes on été traitées par l'ivermectine et suivies pendant 72 heures selon un protocole normalisé, afin de détecter l'apparition d'éventuelles réactions indésirables. Le traitement a été administré à 60% de l'ensemble de la population recensée. Les principales raisons de non-traitement ont été l'application des critères d'exclusion et le fait que certaines personnes étaient absentes du village au moment du traitement. Parmi les personnes traitées, 9% ont fait état de réactions indésirables, 2,4% de réactions modérées et 0,24% de réactions graves. Les réactions signalées étaient généralement du même type que lors des essais cliniques:

douleurs, fièvre, démangeaisons, éruptions cutanées, lymphadénopathie et œdème des membres. Deux effets qui n'avaient jamais été signalés auparavant, à savoir des ganglions inguinaux douloureux et un œdème calleux des membres pourraient être une cause importante de morbidité.

L'incidence des réactions indésirables était directement liée à la charge microfilarienne cutanée, ce qui donne à penser que ces réactions pourraient être dues à l'effet microfilaricide du médicament et non à sa toxicité intrinsèque. La relation avec la charge microfilarienne explique pourquoi l'incidence des réactions était beaucoup plus élevée dans les foyers à forte endémicité. Après correction des résultats pour tenir compte de l'intensité de l'infestation, aucune différence n'a été constatée entre les régions.

La réaction grave la plus fréquente (49 cas) a été l'hypotension orthostatique symptomatique sévère, également liée à la charge microfilarienne. Neuf de ces cas ont nécessité une injection intraveineuse d'hydrocortisone et tous se sont améliorés rapidement, généralement en quelques heures. Les cas les plus graves ont été ceux de trois patients qui ont été atteints d'une dyspnée sévère qui aurait pu être fatale, mais la relation entre cette réaction et le traitement par l'ivermectine est incertaine.

La majorité des effets secondaires et presque toutes les réactions graves se sont produits le lendemain du traitement. Quelques réactions retardées, notamment des œdèmes, ont été signalées lors des visites de suivi, deux et quatre semaines plus tard. Aucun décès n'est survenu pendant la période de suivi chez les patients traités.

Le traitement par l'ivermectine a entraîné une réduction d'environ 98% de la charge microfilarienne moyenne, indépendamment du niveau d'endémicité. Cette diminution massive du nombre de microfilaires et la réduction corrélative du risque de complications onchocerquiennes ont compensé largement l'inconfort temporaire dû aux effets secondaires, qui dans tous les cas ont pu être traités rapidement et avec succès par les équipes de surveillance. On peut donc conclure que l'ivermectine est suffisamment sûre pour être utilisée à grande échelle dans le traitement de l'onchocercose, mais il est recommandé que des infirmières soient présentes sur place pour surveiller les patients pendant au moins 36 heures.

References

1. **Aziz, M.A. et al.** Efficacy and tolerance of ivermectin in human onchocerciasis. *Lancet*, **2**: 171–173 (1982).
2. **Greene, B.M. et al.** Comparison of ivermectin and diethylcarbamazine in the treatment of onchocerciasis. *New England journal of medicine*, **313**: 133–138 (1985).
3. **Larivière, M. et al.** Double-blind study of ivermectin and diethylcarbamazine in African onchocerciasis patients with ocular involvement. *Lancet*, **2**: 174–177 (1985).
4. **Awadzi, K. et al.** The chemotherapy of onchocerciasis. XI. A double-blind comparative study of ivermectin, diethylcarbamazine and placebo in human onchocerciasis in northern Ghana. *Annals of tropical medicine and parasitology*, **80**: 433–442 (1986).
5. **Diallo, S. et al.** A double-blind comparison of the effectiveness and safety of ivermectin and diethylcarbamazine in a placebo-controlled study of Senegalese patients with onchocerciasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **80**: 927–934 (1986).
6. **White, A.T. et al.** Controlled trial and dose-finding study of ivermectin for treatment of onchocerciasis. *Journal of infectious diseases*, **156**: 463–470 (1987).
7. WHO Technical Report Series, No. 597, 1976 (*Epidemiology of onchocerciasis*: report of a WHO Expert Committee).
8. **Merck, Sharp & Dohme.** *Mectizan™, Product monograph.* Rahway, Merck & Co., 1988.
9. **Prost, A & Prod'hon, J.** Le diagnostic parasitologique de l'onchocercose: revue critique des methodes en usage. *Médecine tropicale*, **38**: 519–532 (1978).
10. **Remme, J. et al.** A force-of-infection model for onchocerciasis and its applications in the epidemiological evaluation of the Onchocerciasis Control Programme in the Volta River Basin area. *Bulletin of the World Health Organization*, **64**: 667–681 (1986).
11. **Awadzi, K.** The chemotherapy of onchocerciasis. II. Quantitation of the clinical reaction to microfilaricides. *Annals of tropical medicine and parasitology*, **74**: 189–197 (1980).
12. **De Sole, G. et al.** A community trial of ivermectin in the onchocerciasis focus of Asubende, Ghana. II. Adverse reactions. *Tropical medicine and parasitology*, **40**: 375–382 (1989).
13. **Remme, J. et al.** A community trial of ivermectin in the onchocerciasis focus of Asubende, Ghana. I. Effect on the microfilarial reservoir and the transmission of *Onchocerca volvulus*. *Tropical medicine and parasitology*, **40**: 307–374 (1989).